Tapinarof Cream 1% Once Daily for the Treatment of Moderate to Severe Atopic Dermatitis in Children and Adults: The Pivotal Phase 3 ADORING Clinical Program

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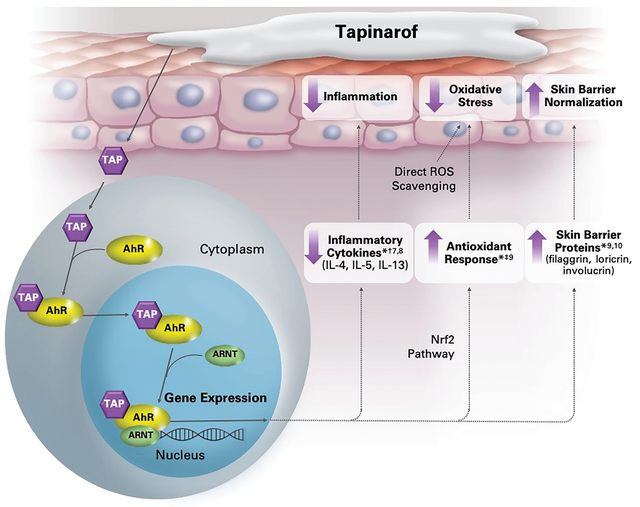
SYNOPSIS

- Atopic dermatitis (AD) is a chronic, relapsing, and remitting inflammatory skin disease characterized by intense pruritus and eczematous lesions that can substantially impact sleep and quality of life[1–4]
- In the US, approximately 16.5 million adults and 9.6 million children under the age of 18 years have AD[5]
- There is a need for efficacious non-steroidal topical therapies for AD without restrictions on duration, extent or site of use
- Tapinarof is a novel, first-in-class, small-molecule topical therapeutic aryl hydrocarbon receptor modulating agent (TAMA) in development for the treatment of AD and psoriasis. Tapinarof has demonstrated efficacy and a remittive effect in Phase 3 clinical trials for the treatment of plaque psoriasis: PSOARING 1 (NCT03956355), PSOARING 2 (NCT03983980), and PSOARING 3 (NCT04053387)
- Tapinarof specifically binds to and activates the aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor. This leads to the downregulation of inflammatory Th2 cytokines (including interleukin [IL]-4, IL-5 and IL-13), increase in expression of skin barrier proteins related to keratinocyte differentiation, including filaggrin, loricrin, and involucrin, and antioxidant activity[6–10] (**Figure 1**)

Figure 1. Potential Mechanisms of Action of Tapinarof in Atopic Dermatitis



*Demonstrated *in vitro*. †Demonstrated in mouse models. ‡Demonstrated *ex vivo*. AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; IL, interleukin; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TAP, tapinarof.

- Tapinarof cream 1% once daily (QD) demonstrated significant efficacy versus vehicle at 12 weeks and was well tolerated in adolescents and adults with moderate to severe AD in a Phase 2b trial (NCT02564055). Efficacy was generally maintained through the last study visit, 4 weeks after completing treatment, warranting further investigation of a potential remittive effect; this will be defined as the maintenance of disease control (a validated Investigator Global Assessment for Atopic Dermatitis™ [vIGA-AD™] score of 0 [clear] or 1 [almost clear]) off therapy[11,12]

OBJECTIVE

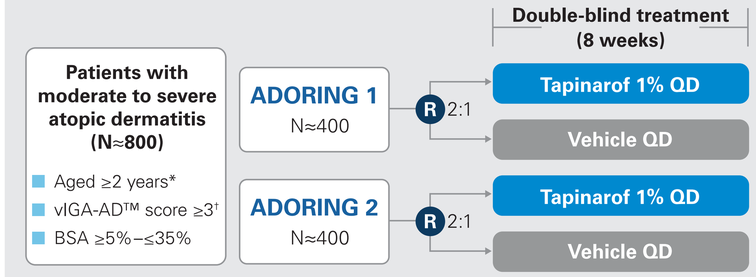
- To assess the efficacy and safety of tapinarof cream 1% QD in children and adults with moderate to severe AD in the two pivotal Phase 3 studies (ADORING 1 and 2) and a long-term extension Phase 3 trial (ADORING 3)

METHODS

Trial Design: ADORING 1 and 2

- ADORING 1 and ADORING 2 are two identically designed, Phase 3, multicenter (US and Canada), double-blind, vehicle-controlled randomized trials (**Figure 2**)
- Following a 30-day screening period, patients aged ≥2 years old with an vIGA-AD score ≥3 (moderate to severe) and a percentage body surface area (%BSA) affected of ≥5–≤35% will be randomized 2:1 to tapinarof cream 1% QD or vehicle QD for 8 weeks

Figure 2. Trial Design: ADORING 1 and ADORING 2



*A minimum of approximately 15% of patients will be enrolled into each of the following age groups: 2–6 years, 7–11 years, 12–17 years, and ≥18 years. Adults (≥18 years) will comprise a maximum of approximately 20% of enrolled patients. †Patients with a vIGA-AD score of 4 (severe) will represent a minimum of approximately 10% of the total randomized population; the remainder of the population will have a vIGA-AD score of 3 (moderate).
Prohibited concomitant medications (and washout periods prior to baseline) include monoclonal antibody products approved for AD (4 months), non-topical corticosteroids or immunosuppressants (28 days), and topical PDE4 inhibitors, tacrolimus ointment, pimecrolimus cream, medium- or high-potency topical corticosteroids or coal tar (all 14 days).
BSA, body surface area; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis™; PDE4, phosphodiesterase-4; QD, once daily; R, randomized.

Statistical Analysis

- Efficacy endpoints analyzed from the intention-to-treat (ITT) population using multiple imputation for missing data. Safety endpoints analyzed based on the safety population, defined as all randomized subjects who receive at least 1 application of study drug
- For categorical endpoints, *P*-values for differences between tapinarof cream 1% QD and vehicle calculated using Cochran-Mantel-Haenszel analysis and stratified by baseline vIGA-AD score and age group. *P*-values for continuous variables calculated using analysis of covariance, with baseline vIGA-AD score and age group as covariates and baseline value as a continuous covariate

Efficacy Endpoints

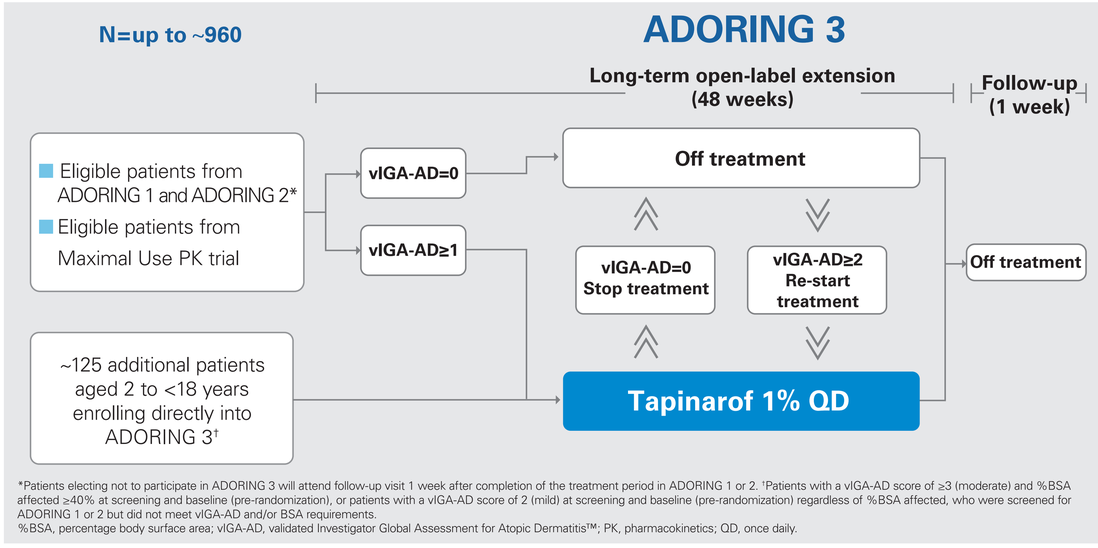
- Primary efficacy endpoint is the proportion of patients with a vIGA-AD score of 0 (clear) or 1 (almost clear) and ≥2-grade improvement from baseline at Week 8
- Secondary efficacy endpoints from baseline at Week 8:
  - Proportion who achieve ≥75% improvement in Eczema Area and Severity Index (EASI75)
  - Mean change in %BSA affected
  - Proportion who achieve ≥90% improvement in EASI (EASI90)
  - Proportion of patients aged ≥12 years with a baseline Peak Pruritus – Numeric Rating Scale (PP-NRS) score ≥4, who achieve ≥4-point reduction in the PP-NRS

Safety and Tolerability Endpoints

- Incidence, frequency and nature of treatment-emergent adverse events and serious adverse events
- Laboratory values, vital signs, and electrocardiograms
- Patient- and investigator-assessed local tolerability

Trial Design: ADORING 3

- ADORING 3 is a long-term, open-label, multicenter extension trial to evaluate the long-term safety and efficacy of tapinarof 1% QD in patients with AD (**Figure 3**)
- Eligible patients completing ADORING 1, ADORING 2, or the Maximal Use Pharmacokinetics trial can enroll in ADORING 3
- In addition, approximately 125 pediatric patients (aged 2 to <18 years) can enroll directly in ADORING 3 if they had a vIGA-AD score of ≥3 (moderate) and %BSA affected ≥40% at screening and baseline (pre-randomization), or patients with a vIGA-AD score of 2 (mild) at screening and baseline (pre-randomization) regardless of %BSA affected, and were thus not eligible for participation in the ADORING 1 and 2 pivotal trials



*Patients electing not to participate in ADORING 3 will attend follow-up visit 1 week after completion of the treatment period in ADORING 1 or 2. †Patients with a vIGA-AD score of ≥3 (moderate) and %BSA affected ≥40% at screening and baseline (pre-randomization), or patients with a vIGA-AD score of 2 (mild) at screening and baseline (pre-randomization) regardless of %BSA affected, who were screened for ADORING 1 or 2 but did not meet vIGA-AD and/or BSA requirements.
%BSA, percentage body surface area; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis™; PK, pharmacokinetics; QD, once daily.

Figure 3. Trial Design: ADORING 3

- In ADORING 3, patients will be treated based on their vIGA-AD score:
  - Patients entering with, or achieving, a vIGA-AD score of 0 (clear) will discontinue treatment and will be monitored for remittive effect, defined as off therapy maintenance of a vIGA-AD score of 0 (clear) or 1 (almost clear)
  - Patients entering with a vIGA-AD score ≥1 (almost clear) will receive tapinarof 1% QD until they achieve complete disease clearance, defined as a vIGA-AD score of 0 (clear)

METHODS (continued)

Trial Design: ADORING 3 (continued)

  - If disease worsening occurs (defined as a vIGA-AD score ≥2 [mild]), tapinarof 1% QD will be started and continued until a vIGA-AD score of 0 (clear) is achieved
- Treatment and re-treatment will continue until the end of the study

Endpoints and Statistical Analysis: ADORING 3

- **Safety and tolerability endpoints:** Adverse events, patient- and investigator-assessed local tolerability, laboratory values, vital signs, and physical exams
- **Efficacy endpoints include:**
  - **Complete disease clearance:** Proportion of patients achieving vIGA-AD of 0 (clear)
  - **Remittive effect:** Duration of efficacy maintenance, vIGA-AD of 0 (clear) or 1 (almost clear) while off therapy, after achieving complete disease clearance (vIGA-AD=0)
  - **Response:** Proportion of patients who enter the trial with a vIGA-AD≥2 (mild) and achieve a vIGA-AD of 0 (clear) or almost clear (1)
  - **Durability of response (absence of tachyphylaxis on therapy):** Maintenance of efficacy on treatment
- Efficacy endpoints will be based on the ITT population using observed case and last observation carried forward analyses. Safety endpoint analysis will be based on the ITT population

CONCLUSIONS

- **This comprehensive Phase 3 clinical trial program will assess the efficacy, safety, tolerability, durability, and potential remittive effect of tapinarof cream 1% QD for the treatment of moderate to severe AD in patients down to 2 years of age**

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